ACTION OF BARIUM AND POTASSIUM IONS ON MEMBRANE POTENTIAL FLUCTUATIONS OF RAT PAPILLARY CARDIOMYOCYTES

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Overloading of cardiomyocytes with Ca ions in the resting state leads to oscillations of tone (mechanical noise — MN) and membrane potential fluctuations (MPF). They are considered to be caused by fluctuations of the intracellular Ca^{++} concentration due to cyclic activity of the sarcoplasmic reticulum [4, 6, 10, 13]. In rat myocardial preparations MN and MPF have been found under control conditions also, and the MN recorded from the muscle ends consisted of aperiodic fluctuations of tone [1, 2, 5]. The writers showed previously that Ba^{++} ions, synchronizing local mechanical noise of the rat papillary muscle, changes the character of the global MN, making it sinusoidal in the period preceding the first spontaneous excitation. It has been suggested that this process is based on synchronization of MPF of single cells of the preparation, caused by the action of Ba ions on the length constant (λ) [3, 9].

The aim of the present investigation was to obtain experimental proof of the role of the passive properties of the membrane during synchronization of the cell noise activity of the myocardial preparation under the influence of Ba ions. Besides Ba^{++}, other factors modifying the value of λ also were investigated: membrane depolarization and an increase in the K^+ ion concentration [11, 12].

EXPERIMENTAL METHOD

Experiments were carried out at T = 22°C on papillary muscles isolated from the right ventricle of the rat heart. The preparation was adapted for 1 h with a frequency of stimulation of 42 pulses/min until the force of contraction was stabilized. The muscle was then stretched to a resting voltage of 10 mN/mm^2 and stimulation was stopped. The composition of the perfusion fluid, the experimental conditions, and the method of recording global MN of the muscle were described previously [4, 5]. Simultaneously with the global MN, the membrane potential of the myocyte was recorded by means of a "floating" microelectrode. The mean amplitude of electrical noise of the recording system did not exceed 20 μV. MPF were obtained by increasing the resting potential of the cell within the frequency range 0.2-10 Hz. The power spectrum of MPF was calculated for a cut of the recording 51.2 sec in duration by means of a laboratory computer, using the algorithm of a rapid Fourier transform [7]. The frequency of digitization of data was 20 Hz. In some experiments a current was passed through the muscle by means of a glass micropipet filled with physiological saline (diameter of tip about 10 μ, resistance under 1 MΩ), touching the surface of the preparation. The current was passed by means of a Dagan-8500 amplifier (USA). In these experiments the membrane potential was recorded at a distance of not more than 1 mm from the current electrode, and to minimize the artefact, the indifferent electrode was placed in the immediate vicinity of the active electrode. The strength of the current passed did not depend on the resistance of the micropipet (current clamping conditions). MN and MPF were recorded on a "Gould—Brush 2400" automatic writer (USA).

EXPERIMENTAL RESULTS

A simultaneous trace of MN of the muscle and MPF of a myocyte tested under control conditions is given in Fig. 1a. No correlation was found between MN and MPF under these conditions.

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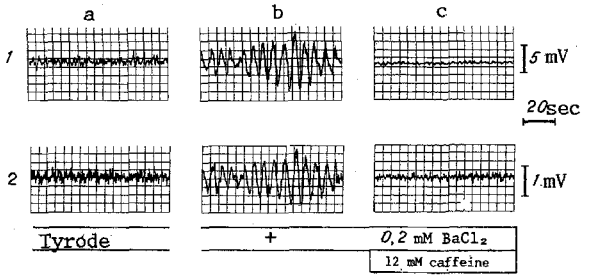

Fig. 1. Changes in MPF (1) and MN (2) under the influence of barium; experiment on June 26, 1985. Explanation in text.

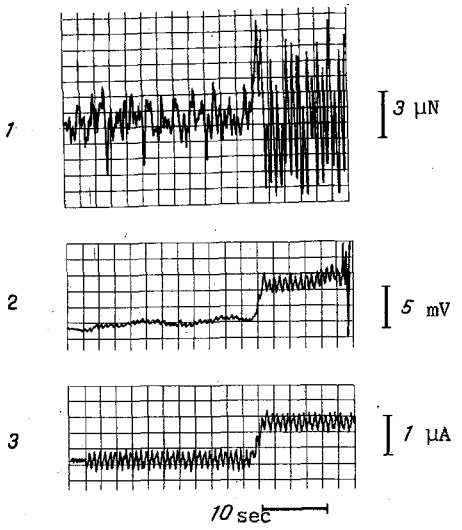

Fig. 2. Action of a sinusoidal current (3) passed at the resting potential level and during depolarization, on membrane potential (2) and MN (1); experiment on October 11, 1984.

Addition of 200 μM $BaCl_2$ to the perfusion fluid, a concentration too low to induce natural rhythmic activity, led to slight (by about 5 mV) membrane depolarization, a gradual increase in the amplitude of MN and MPF, and the establishment of close correlation between them. In the presence of Ba^{++}, MN and MPF became sinusoidal in shape (Fig. 1b). Similar relations between membrane potential and MN were recorded in the period before spontaneous excitation under the influence of 1 mM $BaCl_2$ [3]. Caffeine, which blocks functions of the sarcoplasmic reticulum [8], depressed both MN and MPF (Fig. 1c). It may thus be suggested that the cyclic activity of the sarcoplasmic reticulum lies at the basis of MN and MPF, modified by the action of Ba ions.

Membrane depolarization, caused by passage of a current [11], is known to lead to an increase in membrane resistance and, consequently, to an increase in λ. In a series of experiments the effect of depolarization of the cell membrane on MN and MPF was studied. Depolarization was induced by passing a current through the muscle. Just as during the action of Ba^{++}, slight (10-15 mV) depolarization led to an increase in amplitude, to the appearance of close correlation, and to a sinusoidal character of MN and MPF. On further depolarization of the preparation spontaneous activity developed. To confirm that an increase in λ leads to improvement of intercellular electrotonic interaction, a sinusoidal current was passed through the micropipet in contact with the muscle surface (Fig. 2). The frequency of the sinusoid was 1 Hz, a value comparable with the frequency of MPF recorded in the presence of Ba^{++}. It will be clear from Fig. 2 that passage of a sinusoidal current at the resting potential level had virtually no effect on MN or membrane potential. With slight depolarization of the preparation the sinusoid could already be clearly seen on the trace of membrane potential and MN.

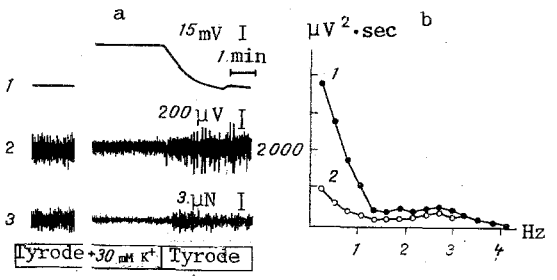

Fig. 3. Action of a high potassium concentration on MPF. a) Simultaneous recording of membrane potential (1), MPF (2), and MN (3); experiment on June 3, 1985; b) change in power spectrum under the influence of 30 mM KCl (2); 1) control.

Further depolarization of the preparation led to natural rhythmic activity, the first cycles of which had a frequency equal to that of the sinusoidal current. This experiment can be regarded as a model of the process of involvement of an ever-increasing number of myocytes in synchronous activity during an increase in λ. In some experiments the effects of a sinusoidal current passed in the control and in the presence of 100 μM Ba^{++} was compared. The experiments showed that the amplitude of the sinusoidal current which did not change MN of the muscle in the control induced corresponding fluctuations of tone in the presence of Ba^{++}.

Another factor leading to depolarization, but reducing λ is an increase in the K^+ concentration in the perfusion fluid [11, 12]. We studied the effect of a high KCl concentration of MPF and MN (Fig. 3a). It will be clear from Fig. 3 that an increase in K^+ led to membrane depolarization and to a decrease in the amplitudes of MPF and MN. The reduction in MPF in this case took place on account of a fall in the amplitudes of the nonresonance components of the power spectrum (Fig. 3b). It can accordingly be concluded that the nonresonance component of the spectrum of MPF reflects the contribution of the electrotonic influence of MPF of neighboring cells. The resonance frequency in the MPF spectrum in the control is of a different nature from the resonance frequency of MPF under the influence of Ba^{++}, for their frequencies differ by almost an order of magnitude. It can be postulated that the resonance frequency of MPF in the control coincides with the characteristic frequency of cyclic activity of the sarcoplasmic reticulum of the single cell. Under the influence of Ba^{++}, MPF reflect synchronous activity of many cells of the muscle, depending on the characteristics of electrotonic interaction.

These experiments thus showed that the amplitude and character of MPF and MN depend strongly on the passive properties of the cell membrane. Factors which increase λ lead to the appearance of resonance oscillations on MPF and MN, whereas factors reducing λ lead to a fall in the amplitudes of MPF and MN. In the absence of stimulation Ba^{++} induces spontaneous activity of the rat papillary muscle which resembles in type the appearance of oscillatory prepotentials of gradually increasing amplitude [3]. A similar picture was observed during the action of Ba^{++} on Purkinje fibers [14]. We concluded that development of barium automatism is preceded by a period of synchronization of electrical activity of single cells of the preparation. The synchronization process takes place on account of the mutual electrotonic influence of neighboring myocardial cells, and for that reason a special role is played here by passive electrical characteristics of the preparation. The increase in λ evoked by Ba^{++} is evidence of the main cause of synchronization of noise activity in the period preceding spontaneous excitation of the myocardial preparation.

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EFFECT OF NORADRENALIN ON REACTIVE MYOCARDIAL HYPEREMIA IN DOGS

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Under the influence of noradrenalin (NA) the coronary vessels undergo predominantly vasodilatation in response to an increase in the work of the heart and the intensity of its metabolism [4]. Comparison of responses of the coronary vessles and the oxygen consumption (with administration of NA and isoproterenol) showed that the magnitude of the dilator response lags behind that of the oxygen consumption in response to NA but precedes vasodilatation in response to isoproterenol [6]. Chronic experiments [2, 7] showed that injection of NA, with constant cardiac rhythm, induces a biphasic response of the coronary vessels with transient initial dilatation of the coronary vessels followed by their prolonged constriction. However, the effect of NA on coronary vascular tone in the period of ischemia and reactive hyperemia (RH) remains unclear, although we know that β-adrenergic blockade leads to a reduction of myocardial RH whereas, on the contrary, α-adrenergic blockade increases RH [5].

In the investigation described below the effect of NA on dilatation of the coronary vessels during RH was investigated in more detail.

EXPERIMENTAL METHOD

Experiments were carried out on 9 dogs, weighing 12 kg on average, under hexobarbital anesthesia with morphine premedication (75 and 5 mg/kg body weight, respectively). Thoracotomy was performed in the 5th intercostal space and the animal was artificially ventilated on the RO-3 apparatus. The pressure in the left ventricle was measured by means of a catheter introduced through its wall into its lumen. To stabilize the blood pressure (BP) a cannula connected to a reservoir was introduced through the brachiocephalic artery into the ascending aorta. The pressure in the arterial system and left ventricle was measured by means of a Hewlett-Packard transducer. The coronary blood flow was measured by means of a Statham SP 2201 electromagnetic flowmeter in the circumflex or descending branch of the left coronary artery (lay-on transducers 2-3 mm in diameter). The coronary blood flow was arrested for 20 sec at the beginning of development of the cardiac response to injection of NA (series I), and also after injection of NA, as soon as the parameters of the cardiodynamics had returned

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